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For the use of a Registered Medical Practitioner or a Hospital or a Laboratory

VALZAAR

(Valsartan Tablets, 40 mg & 80 mg)

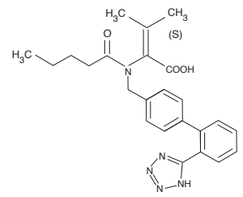
COMPOSITION

VALZAAR 40: Each film-coated tablet contains Valsartan USP.... 40 mg
VALZAAR 80: Each film-coated tablet contains Valsartan USP.... 80 mg

DESCRIPTION

Valzaar is an orally active, nonpeptide and specific angiotensin II receptor blocker acting on the AT1 receptor subtype.

Valsartan is chemically N-(1-oxopentyl)-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl] methyl]-L-valine. Its empirical formula is $C_{24}H_{29}N_5O_3$, and its molecular weight is 435.5. Its structural formula is



Valzaar is available as tablets for oral administration, containing either 40 mg, 80 mg or of valsartan.

CLINICAL PHARMACOLOGY

Mechanism of action

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin- angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT2 receptor found in many tissues, but AT2 is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT1 receptor than for the AT2 receptor. The increased plasma levels of angiotensin II following AT1 receptor blockade with valsartan may stimulate the unblocked AT2 receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT1 receptor about one 200th that of valsartan itself.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because valsartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known.

Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of valsartan on blood pressure.

Pharmacokinetics

Peak plasma concentration of valsartan is reached within 2 to 4 hours after dosing. Valsartan shows biexponential decay kinetics following intravenous administration, with an average elimination half-life of about 6 hours. Absolute bioavailability for valsartan is about 25% (range 10%-35%).

Food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (Cmax) by about 50%. AUC and Cmax values of valsartan increase approximately linearly with increasing dose over the clinical dosing range. Valsartan does not accumulate appreciably in plasma following repeated administration.

Distribution

The steady state volume of distribution of valsartan after intravenous administration is small (17 L). Valsartan is highly bound to serum proteins (95%), mainly serum albumin.

Metabolism and Elimination

When administered as an oral solution, about 83% is excreted in the faeces and 13% in the urine, mainly as unchanged compound. The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan.

Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance).

Special Populations

Pediatric: The pharmacokinetics of valsartan have not been investigated in patients < 18 years of age.

Geriatric: As measured by the AUC, exposure to valsartan is higher by 70% and the half-life is longer by 35% in the elderly than in the young. No dosage adjustment is necessary.

Gender: Pharmacokinetics of valsartan does not differ significantly between males and females.

Heart Failure: The average time to peak concentration and elimination half-life of valsartan in heart failure patients are similar to that observed in healthy volunteers. AUC and Cmax values of valsartan increase linearly and are almost proportional with increasing dose over the clinical dosing range (40 to 160 mg twice a day). The average accumulation factor is about 1.7. The apparent clearance of valsartan following oral administration is approximately 4.5 L/h. Age does not affect the apparent clearance in heart failure patients.

Renal Insufficiency: Dose adjustment is not required in patients with mild-to-moderate renal dysfunction. No studies have been performed in patients with severe impairment of renal function (creatinine clearance < 10 mL/min). Valsartan is not removed from the plasma by hemodialysis.

Hepatic Insufficiency: Patients with mild-to-moderate chronic liver disease have nearly twice the exposure to valsartan as compared to healthy volunteers (matched by age, sex and weight). In general, no dosage adjustment is needed in patients with mild-to-moderate liver disease. Care should be exercised in patients with liver disease.

Pharmacodynamics and Clinical effects

Hypertension

Valsartan inhibits the pressor effect of angiotensin II infusions. An oral dose of 80 mg inhibits the pressor effect by about 80% at peak with approximately 30% inhibition persisting for 24 hours. No information on the effect of larger doses is available.

Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin and consequent rise in angiotensin II plasma concentration in hypertensive patients.

Minimal decreases in plasma aldosterone were observed after administration of valsartan; very little effect on serum potassium was observed.

In multiple-dose studies in hypertensive patients with stable renal insufficiency and patients with renovascular hypertension, valsartan had no clinically significant effects on glomerular filtration rate, filtration fraction, creatinine clearance, or renal plasma flow.

In multiple-dose studies in hypertensive patients, valsartan had no notable effects on total cholesterol, fasting triglycerides, fasting serum glucose, or uric acid.

The antihypertensive effects of Valsartan were demonstrated principally in 7 placebocontrolled, 4- to 12-week trials (one in patients over 65) of dosages from 10 to 320 mg/day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparison of once-daily and twice-daily regimens of 160 mg/day; comparison of peak and trough effects; comparison (in pooled data) of response by gender, age, and race; and evaluation of incremental effects of hydrochlorothiazide.

Administration of valsartan to patients with essential hypertension results in a significant reduction of sitting, supine, and standing systolic and diastolic blood pressure, usually with little or no orthostatic change.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs at approximately 2 hours, and maximum reduction of blood pressure is achieved within 6 hours. The antihypertensive effect persists for 24 hours after dosing, but there is a decrease from peak effect at lower doses (40 mg) presumably reflecting loss of inhibition of angiotensin II. At higher doses, however (160 mg), there is little difference in peak and trough effect. During repeated dosing, the reduction in blood pressure with any dose is substantially present within 2 weeks, and maximal reduction is generally attained after 4 weeks. In long-term follow-up studies (without placebo control), the effect of valsartan appeared to be maintained for up to two years. The antihypertensive effect is independent of age, gender or race. The latter finding regarding race is based on pooled data and should be viewed with caution, because antihypertensive drugs that affect the renin-angiotensin system (that is, ACE inhibitors and angiotensin-II blockers) have generally been found to be less effective in low-renin hypertensives (frequently blacks) than in high-renin hypertensives (frequently whites). In pooled, randomized, controlled trials of Valsartan that included a total of140 blacks and 830 whites, valsartan and an ACE-inhibitor control were generally at least as effective in blacks as whites. The explanation for this difference from previous findings is unclear.

Abrupt withdrawal of valsartan has not been associated with a rapid increase in blood pressure.

The blood pressure lowering effect of valsartan and thiazide-type diuretics are approximately additive.

The 7 studies of valsartan monotherapy included over 2,000 patients randomized to various doses of valsartan and about 800 patients randomized to placebo. Doses below 80 mg were not consistently distinguished from those of placebo at trough, but doses of 80, 160 and 320 mg produced dose-related decreases in systolic and diastolic blood pressure, with the difference from placebo of approximately 6-9/3-5 mmHg at 80-160 mg and 9/6 mmHg at 320 mg. In a controlled trial the addition of HCTZ to valsartan 80 mg resulted in additional lowering of systolic and diastolic blood pressure by approximately 6/3 and 12/5 mmHg for 12.5 and 25 mg of HCTZ, respectively, compared to valsartan 80 mg alone.

Patients with an inadequate response to 80 mg once daily were titrated to either 160 mg once daily or 80 mg twice daily, which resulted in a comparable response in both groups.

In controlled trials, the antihypertensive effect of once-daily valsartan 80 mg was similar to that of once-daily enalapril 20 mg or once-daily lisinopril 10 mg.

There was essentially no change in heart rate in valsartan-treated patients in controlled trials.

Heart Failure

The Valsartan Heart Failure Trial (Val-HeFT) was a multinational, double-blind study in which 5,010 patients with NYHA class II (62%) to IV (2%) heart failure and LVEF < 40%, on baseline therapy chosen by their physicians, were randomized to placebo or valsartan (titrated from 40 mg twice daily to the highest tolerated dose or 160 mg twice daily) and followed for a mean of about 2 years. Although Val-HeFT.s primary goal was to examine the effect ofvalsartan when added to an ACE inhibitor, about 7% were not receiving an ACE inhibitor. Other background therapy included diuretics (86%), digoxin (67%), and beta- blockers (36%). The population studied was 80% male, 46% 65 years or older and 89% Caucasian. At the end of the trial, patients in the valsartan group had a blood pressure that was 4 mmHg systolic and 2 mmHg diastolic lower than the placebo group. There were two primary end points, both assessed as time to first event: all-cause mortality and heart failure morbidity, the latter defined as all-cause mortality, sudden death with resuscitation, hospitalization for heart failure, and the need for intravenous inotropic or vasodilatory drugs for at least 4 hours.

INDICATIONS

Hypertension

Valzaar is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

Heart failure

Valzaar is indicated for the treatment of heart failure (NYHA class II-IV) in patients who are intolerant of angiotensin converting enzyme inhibitors.

DOSAGE AND ADMINISTRATION

Hypertension

The recommended starting dose of Valzaar (valsartan) is 80 mg or 160 mg once daily when used as monotherapy in patients who are not volume-depleted. Patients requiring greater reductions may be started at the higher dose. Valzaar may be used over a dose range of 80 mg to 320 mg daily, administered once-a-day.

The antihypertensive effect is substantially present within 2 weeks and maximal reduction is generally attained after 4 weeks. If additional antihypertensive effect is required over the starting dose range, the dose may be increased to a maximum of 320 mg or a diuretic may be added. Addition of a diuretic has a greater effect than dose increases beyond 80 mg.

No initial dosage adjustment is required for elderly patients, for patients with mild or moderate renal impairment, or for patients with mild or moderate liver insufficiency.

Valzaar may be administered with other antihypertensive agents. Valzaar may be administered with or without food.

Heart Failure

The recommended starting dose of valsartan is 40 mg twice daily. Uptitration to 80 mg and 160 mg twice daily should be done to the highest dose, as tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 320 mg in divided doses. Concomitant use with an ACE inhibitor and a beta-blocker is not recommended.

CONTRAINDICATIONS

Valsartan is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

Foetal/ Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause foetal and neonatal morbidity and death when administered to pregnant women.

When pregnancy is detected, valsartan should be discontinued as soon as possible.

Hypotension

Rare cases of excessive hypotension have been reported in patients with uncomplicated hypertension treated with valsartan alone. In volume- and/or salt-depleted patients receiving high doses of diuretics, valsartan administration may result in symptomatic hypotension.

Volume- and/or salt-depletion should be corrected prior to administration of valsartan, or the treatment should start under close medical supervision.

If excessive hypotension occurs, the patient should be placed in a supine position and, if necessary, given an intravenous infusion of normal saline. Valsartan treatment can usually be continued without difficulty once the blood pressure has stabilized.

Hypotension in Heart Failure Patients

Valsartan therapy should be initiated with caution in patients with heart failure. Patients with heart failure given valsartan may have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary.

PRECAUTIONS

General

Impaired Hepatic Function: As valsartan is eliminated mainly in the bile care should be exercised in administering valsartan to patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders.

Impaired Renal Function - Hypertension: Use of ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis has been associated with increases in serum creatinine or blood urea nitrogen. An effect similar to that seen with ACE inhibitors should be anticipated with the use of valsartan.

Impaired Renal Function - Heart Failure: In patients with severe heart failure whose renal function may depend on the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers has been associated with oliguria and/or progressive azotemia and with acute renal failure (rarely) and/or death. Some patients with heart failure have developed increases in blood urea nitrogen, serum creatinine, and potassium. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or valsartan may be required.

Concomitant Therapy in Patients with Heart Failure: In patients with heart failure, concomitant use of valsartan, an ACE inhibitor, and a beta-blocker is not recommended. In the Valsartan Heart Failure Trial, this triple combination was associated with an unfavorable heart failure outcome.

Drug Interactions

No clinically significant pharmacokinetic interactions have been reported with the concurrent administration of valsartan with amlodipine, atenolol, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. Used together with cimetidine, the systemic exposure of valsartan may be marginally increased.

Co-administration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

CYP 450 Interactions: The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes. The inhibitory or induction potential of valsartan on CYP 450 is also unknown.

As with other angiotensin receptor blockers, concomitant use of potassium sparing diuretics, potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine.

Carcinogenesis, Mutagenesis and Impairment of Fertility

There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at doses up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.6 and 6 times, respectively, the maximum recommended human dose on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

Mutagenicity assays did not reveal any valsartan-related effects at either the gene or chromosome level.

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/ m^2 basis.

Pregnancy and Lactation

As for any drug that also acts directly on the renin-angiotensin-aldosterone system, Valzaar should not be used during pregnancy. If pregnancy is detected during therapy, Valzaar should be discontinued as soon as possible. It is not known whether valsartan is excreted in human milk. Valsartan was excreted in the milk of lactating rats. Thus, it is not advisable to use Valzaar in lactating mothers.

Paediatric Use

Safety and effectiveness in paediatric patients have not been established.

Geriatric Use

Though no notable differences in safety and efficacy have been reported between older and younger patients, greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

In general in clinical trials, valsartan had a side-effect profile comparable to placebo; adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The most common reasons for discontinuation of therapy with valsartan were headache and dizziness.

The adverse experiences that occurred in placebo-controlled clinical trials in at least 1% of patients treated with valsartan and at a higher incidence in valsartan than placebo patients included viral infection (3% vs. 2%), fatigue (2% vs. 1%), and abdominal pain (2% vs. 1%).

In controlled clinical trials, clinically significant changes in laboratory parameters were rarely seen in patients taking valsartan. In rare cases, valsartan was associated with decreases in haemoglobin and haematocrit; neutropenia was observed occasionally. Increases in serum creatinine have been reported infrequently. In heart failure trials elevations of blood urea nitrogen (BUN) were observed in 16.6% of valsartan-treated patients compared to 6.3% of placebo-treated patients.

Occasional elevation of serum potassium has been reported but rarely has this been of clinical significance. Serum potassium should be monitored in renally impaired or elderly patients if they are also taking potassium supplements.

Adverse events reported during post marketing experience have, in general, been mild and transient in nature. The following have been reported very rarely:

Body as a whole: Fatigue
Cardiovascular: Palpitations
Gastrointestinal: Diarrhoea, flatulence, dyspepsia, liver function abnormalities
Haematological: Thrombocytopenia
Musculoskeletal: Arthralgia, myalgia
Nervous system: Dizziness, headache, mild and transient taste disturbance
Renal: Renal dysfunction and isolated cases of renal impairment Respiratory: Cough, epistaxis
Urogenital: Impotence
Hypersensitivity: Angioedema, rash pruritis and isolated cases of other hypersensitivity/allergic reactions including serum sickness and vasculitis

OVERDOSAGE

Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia. Bradycardia could occur from parasympathetic stimulation. Supportive treatment should be instituted if symptomatic hypotension occurs.

Valsartan is not removed from the plasma by haemodialysis.

Single oral doses of valsartan up to 2000 mg/kg in rats and up to 1000 mg/kg in marmosets, were without grossly observable adverse effects, except for salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 37 times, respectively, the maximum recommended human dose on a mg/m^2 basis).

EXPIRY DATE

Do not use after the date of expiry

STORAGE

Store below 30°C; Protected from light and moisture.

PRESENTATION

Valzaar 40: It is available as Peach coloured, round, biconvex, film coated tablets with break-line on one side in strips of 10 tablets.

Valzaar 80: It is available as Brick red coloured, round biconvex film coated tablets with breakline on one side in strips of 10 tablets.

torrent

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
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